REMARKS

First, applicants respectfully point out that they are well aware that the rejection is based on a combination of documents and believe that the previous response addressed this.

Applicants pointed out in the previous response that the sole independent claim, claim 1, requires the plastic slide claimed as binding to herbal fractions or components be derivatized in a specific manner wherein the coating comprises

1. coupled to the slide, a polyfunctional aldehyde;

2. coupled to the polyfunctional aldehyde a compound that provides at least one NH_2 group;

3. coupled to the NH_2 a polyfunctional epoxide which has at least one epoxide for coupling to the amino group and at least one epoxide for coupling to the herbal fraction or component.

In order to meet all these limitations, it should be evident that Gerster is irrelevant and the Office has been able only, even arguably, to point to these elements using the combination of Chang, Vermeulin, and Cruickshank. Thus, the bulk of the description in the Office action relating to the individual disclosures of Chang and Vermeulin alone is not germane.

Let us then look at what is disclosed in Chang, Vermeulin and Cruickshank, collectively. Chang discloses that extracts can be made from herbs. Vermeulin discloses, as an incidental embodiment of the assays described, a form of the assay where a glutaraldehyde is used to crosslink a polylysine treated plate to a polyamine analog that is the object of the investigation. Cruickshank also, as a disclosure somewhat incidental to the main point, discloses, not plastic chips, but silicon dioxide chips, which are directly derivatized to epoxides and then to nucleic acids. It is unclear to applicants how a combination of a document which teaches that herbs can be extracted, with a document that teaches polylysine coated plate crosslinked with glutaraldehyde to polyamine transport mediators, with a document that describes silicon dioxide chips coupled to an epoxide and then to a nucleic acid results in an herbal chip where a plastic

slide is coupled to a polyfunctional aldehyde coupled to an amine-containing compound coupled in turn to a polyfunctional epoxide coupled in turn to an herbal extract.

Thus, even if these documents are combined, the invention does not result.

Respectfully, there is zero motivation to combine these documents absent hindsight. The only motivation even suggested by the Office is the sentence in the abstract of Vermeulin which says, "The assays of the invention are useful for high throughput screening of targets in the discovery of drugs that interact with a polyamine system." (Nothing about herbal extracts or extracts of any kind.)

It appears that the assays being referred to are those described in column 31, where an assay of polyamine transport is described as a high throughput assay using a fluorescent polyamine-like probe. In this assay, cells are plated in 96-well sterile microplates; this assay has nothing to do with the immobilized polyamine in column 33, cited by the Office. Second, how is a statement that the assays of the invention are useful for the discovery of drugs that interact with the polyamine system motivation to combine a totally different assay in column 33 with a method for presenting herbal components on a chip? And where is the motivation to combine Cruickshank with these documents? The statement quoted by the Office hardly amounts to a motivation to include an epoxide in a chip already derivatized with a polyfunctional aldehyde coupled with an amino group. Further, where is the suggestion in Cruickshank that any chip be used to sort out herbal extracts? The entire combination set forth by the Office is clearly hindsight. If ever there was a classic example of picking and choosing specific passages in unrelated documents using the invention as a guide to piece together the invention after the fact, applicants respectfully submit that this is it.

This is further verified by the enclosed Exhibit A which is a chart and comments prepared by the applicants themselves characterizing the present invention in contrast to the cited documents. The first thing that is evident is that the scope and focus of each of the prior art documents is irrelevant to the presently claimed invention, emphasizing the fact that it would be necessary to have the invention at hand to find any passage in the cited documents that is even

relevant. Thus, as noted in the chart, although the present invention is directed to a method to screen herbal extracts for active ingredients, Chang is devoted to methods to augment an immune response by isolating a specific compound (using column chromatography) from an herbal extract. The focus of Cruickshank is a method for linking a detectable label to a nucleic acid and the focus of Vermeulin is on inhibitors of polyamine transport. As the applicants summarize, there is no teaching to use a microcarrier to allocate herbal components onto a solid support using any technique, nor is there any prior art teaching of the specific sequential coupling processes required by the applicant to display the herbal ingredients for assay, nor is there any prior art teaching to screen the fixed herbal components by labeled probes. None of the cited documents in any way points to the combination of its teachings with the teachings of the other documents cited and collectively the documents fail to teach the invention as claimed.

Gerster is applicable only to claims 10 and 20; applicants do not rely on this additional feature for patentability; nevertheless, the inclusion of Gerster based on a particular section completely unrelated to the thrust of the Gerster document is further evidence of the hindsight nature of this rejection.

CONCLUSION

The sole outstanding rejection appears to be based on a hindsight extraction of obscure portions of unrelated documents. Even putting these obscure portions of the documents together does not result in the invention since the invention requires *plastic* support coupled directly to a *polyfunctional aldehyde* which is coupled to an *amine-providing compound* which is coupled to a *polyfunctional epoxide*, which is coupled to a component of an *herbal extract*. A particular order is required. There is no suggestion in Chang that herbal extracts be coupled to supports of any kind; the supports described by Vermeulin are lysine-coated with an intervening glutaraldehyde coupled to a polyamine that is the test compound itself; and the chips described by Cruickshank are not plastic, but silicon dioxide which are coupled directly to an epoxide and then to a nucleic acid. How those documents can be put together to lead to the invention as claimed is unclear,

even if any motivation to combine them could be shown. Accordingly, applicants respectfully request that the pending claims, claims 1-7, 9-10 and 14-24 be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 205032000500.

Respectfully submitted,

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Exhibit A

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	The invention (Su-Chen Chang, et al.)	US 6,194,563 B1 (Cruickshank)	US 6,172,261 B1 (Vermeulin, et al.)	US 5,753,692 (Chang, et al.)	US 5,714,608 (Gerster)
Title	Herbal chip	Solid phase nucleic acid labeling by transamination	Polyamine analogues as therapeutic and diagnostic agents	Medical thiophene compounds	1-substituted 1H-imidazo-〔4,5-C〕quinolin-4-amines
Scope	A method to screen the herbal ingredients for active ingredients having specific pharmaceutical or therapeutical functions.	A method for linking a detectable label to a nucleic acid	1. Novel inhibitors (polyamine analogues) of polyamine transport. 2. Novel chemical synthetic methods to obtain polyamine analogues. 3. Cell growth assays for high throughput screening.	A method of augmenting the immune system including administering to a subject an effective amount of compounds of a specific formula.	1. The compounds are active as immunomodulators and antiviral agents. 2. Intermediates in the preparation of the said compounds, pharmaceutical compositions and pharmacological methods of use.
Related	1. Allocating the	1. Directly	1. A method for the	1. Compounds	1. Synthesis of the

arts	fractions or components obtained from herbs in microarray on a solid support. 2. The solid support is plastic slide initially coated with polyfunctional aldehyde, then an amino group-providing compound, and finally couples a polyfunctional epoxide to the amino group. 3. Microarraying the herbal components onto the coated plastic slides. Subsequently the herbal components	immobilize nucleic acids on a solid support. 2. The solid support is a bead or chromium-plate d glass slide. 3. Linking a reactive group to the cytidine base of the bound nucleic acid by a transamination reaction. 4. Detectable label linked to the reactive group. 5. Finally cleave the labeled nucleic acids.	synthesis of a polyamine analogue by chain extension. 2. The chain extension reaction comprises attaching a cleavable linker, attaching one or more extender synthons and then attaching a chain terminator. 3. Finally cleave the polyamine chain from the solid support.	purified from the extract of a herb, *Echinops grijisii*, by column chromatography such as HPLC. 2. Methods to synthesize the compounds, thiophenes. 3. The pharmaceutical compositions of the compounds.	compounds of the backbone 1H-imidazo-〔4,5-C〕quinolin-4-amines and its derivatives.

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	will be fixed on the solid support via covalent bonds. 4. The label probes can be added onto the herbal components-containin g chip to test their binding capacity to the labeled probe.				

1. The four cited prior arts references are irrelevant to the invention, based on the ground that:
   A. There is no prior art teaching to use microarryer to allocate herbal components onto a solid support.
   B. There is no prior art teaching the sequentially-coupling processes to make the availability for binding the herbal ingredients, exhibiting molecular diversities.
   C. There is no prior art teaching to screen the fixed herbal components by labeled probes.

2. Cruickshank and Vermeulin taught to fix molecules onto solid support in completely different rationales:
   A. Both the cited references use the selected solid support as an environment for chemical reactions and finally harvest the resultant molecules by chemical cleavages.
   However the sequential coupling process in the said reaction is willing to provide available environment permanently binding with herbal components.
   B. In Cruickshank's art, the materials initially bound to solid supports are nucleic acids instead of herbal components, even the

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solid support was purchased for ready to bind with nucleic acids. The following transamination reaction is selectively occurred on cytidine residues of the bound nucleic acids. Finally the bound nucleic acids are freed by chemical cleavage.

C. Vermeulin et al. also taught a solid-phase method for synthesizing polyamine analogues and these polyamine analogues can be finally cleaved from the solid support. These synthesized polyamine analogues can be used for therapeutic purpose.

D. Gerster taught a completely different art field for synthesizing the derivatives of 1H-imidazo- (4,5-C) quinolin-4-amines. These derivatives of amine analogues may exhibit as immunomodulators and anti-viral agents.

E. The said invention teaching sequential coupling reactions to provide the active functional groups binding with the added herbal components instead of the purpose for synthesis of specific compounds. The herbal components are permanently bound with the solid support. Those ingredients in the herbs, not limited to polyamines analogues, exhibiting capacity binding to the added probes can be hit by using the herbal chips.

3. Chang et al. (US patent 5,753,692) taught a method to isolate highly purified component from an herb, *Echinops grijisii*, by column chromatography. The purified compounds are derivatives of thiophenes. They taught methods to synthesize the thiophene derivatives and demonstrated their activity for pharmaceutical applications.
However, the column chromatography, such as HPLC, is widely applied for fractionating a mixture but not limited to purification of the herbal ingredients. Therefore the art of column chromatography is not related to the either inventions. The said invention taught a new method to immobilize the herbal ingredients onto the solid support that is not taught in Chang's inventions. Neither Chang's invention taught how to promise the herbal components covalently bound with the solid support.
4. In summary, the said invention demonstrated a novel method for screening herbal components in a high throughput. Simply put the cited reference together will not provide solution for improvement the throughput of screening. Even the rationales of the cited references are not related to the screening for the active ingredients from herbs.

Exhibit A
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